



COL4A1-related brain small-vessel disease

COL4A1-related brain small-vessel disease is part of a group of conditions called the *COL4A1*-related disorders. The conditions in this group have a range of signs and symptoms that involve fragile blood vessels. *COL4A1*-related brain small-vessel disease is characterized by weakening of the blood vessels in the brain. Stroke is often the first symptom of this condition, typically occurring in mid-adulthood. In affected individuals, stroke is usually caused by bleeding in the brain (hemorrhagic stroke) rather than a lack of blood flow in the brain (ischemic stroke), although either type can occur. Individuals with this condition are at increased risk of having more than one stroke in their lifetime. People with *COL4A1*-related brain small vessel disease also have leukoencephalopathy, which is a change in a type of brain tissue called white matter that can be seen with magnetic resonance imaging (MRI). Affected individuals may also experience seizures and migraine headaches accompanied by visual sensations known as auras.

Some people with *COL4A1*-related brain small-vessel disease have an eye abnormality called Axenfeld-Rieger anomaly. Axenfeld-Rieger anomaly involves underdevelopment and eventual tearing of the colored part of the eye (iris) and a pupil that is not in the center of the eye. Other eye problems experienced by people with *COL4A1*-related brain small-vessel disease include clouding of the lens of the eye (cataract) and the presence of arteries that twist and turn abnormally within the light-sensitive tissue at the back of the eye (arterial retinal tortuosity). Axenfeld-Rieger anomaly and cataract can cause impaired vision. Arterial retinal tortuosity can cause episodes of bleeding within the eye following any minor trauma to the eye, leading to temporary vision loss.

The severity of the condition varies greatly among affected individuals. Some individuals with *COL4A1*-related brain small-vessel disease do not have any signs or symptoms of the condition.

Frequency

COL4A1-related brain small-vessel disease is a rare condition, although the exact prevalence is unknown. At least 50 individuals with this condition have been described in the scientific literature.

Genetic Changes

As the name suggests, mutations in the *COL4A1* gene cause *COL4A1*-related brain small vessel disease. The *COL4A1* gene provides instructions for making one component of a protein called type IV collagen. Type IV collagen molecules attach to each other to form complex protein networks. These protein networks are the main

components of basement membranes, which are thin sheet-like structures that separate and support cells in many tissues. Type IV collagen networks play an important role in the basement membranes in virtually all tissues throughout the body, particularly the basement membranes surrounding the body's blood vessels (vasculature).

The *COL4A1* gene mutations that cause *COL4A1*-related brain small-vessel disease result in the production of a protein that disrupts the structure of type IV collagen. As a result, type IV collagen molecules cannot attach to each other to form the protein networks in basement membranes. Basement membranes without these networks are unstable, leading to weakening of the tissues that they surround. In people with *COL4A1*-related brain small-vessel disease, the vasculature in the brain weakens, which can lead to blood vessel breakage and stroke. Similar blood vessel weakness and breakage occurs in the eyes of some affected individuals.

Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person has one parent with the condition. Rarely, new mutations in the gene occur in people with no history of the disorder in their family.

Other Names for This Condition

- brain small-vessel disease with hemorrhage

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Brain small vessel disease with hemorrhage
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1843512/>

Other Diagnosis and Management Resources

- GeneReview: COL4A1-Related Disorders
<https://www.ncbi.nlm.nih.gov/books/NBK7046>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>

- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Health Topic: Brain Diseases
<https://medlineplus.gov/braindiseases.html>
- Health Topic: Eye Diseases
<https://medlineplus.gov/eyediseases.html>
- Health Topic: Hemorrhagic Stroke
<https://medlineplus.gov/hemorrhagicstroke.html>
- Health Topic: Migraine
<https://medlineplus.gov/migraine.html>

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Stroke Information Page
<https://www.ninds.nih.gov/Disorders/All-Disorders/Stroke-Information-Page>

Educational Resources

- Cedars-Sinai Medical Center: Cerebral Hemorrhage
<http://www.cedars-sinai.edu/Patients/Health-Conditions/Hemorrhagic-Stroke.aspx>
- Disease InfoSearch: Brain small vessel disease with hemorrhage
<http://www.diseaseinfosearch.org/Brain+small+vessel+disease+with+hemorrhage/7863>
- Johns Hopkins Medicine Department of Neurology and Neurosurgery: Intracerebral Hemorrhage
http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/pediatric_neurovascular/conditions/intracerebral_hemorrhage.html
- Johns Hopkins Medicine Department of Neurology and Neurosurgery: Stroke
http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/cerebrovascular/conditions/stroke.html
- MalaCards: col4a1-related brain small-vessel disease
http://www.malacards.org/card/col4a1_related_brain_small_vessel_disease

- Orphanet: Familial vascular leukoencephalopathy
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=36383
- University of Texas Southwestern Medical Center, Internet Stroke Center: Intracerebral Hemorrhage
<http://www.strokecenter.org/patients/about-stroke/intracerebral-hemorrhage/>

Patient Support and Advocacy Resources

- Family Caregiver Alliance: Stroke
<https://www.caregiver.org/health-issues/stroke>
- Prevent Blindness America
<http://www.preventblindness.org/>

GeneReviews

- COL4A1-Related Disorders
<https://www.ncbi.nlm.nih.gov/books/NBK7046>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22COL4A1-related+brain+small-vessel+disease%22+OR+%22Cerebral+Hemorrhage%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28small+vessel+disease%5BTIAB%5D%29+AND+%28COL4A1%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

OMIM

- BRAIN SMALL VESSEL DISEASE WITH OR WITHOUT OCULAR ANOMALIES
<http://omim.org/entry/607595>

Sources for This Summary

- Lanfranconi S, Markus HS. COL4A1 mutations as a monogenic cause of cerebral small vessel disease: a systematic review. *Stroke*. 2010 Aug;41(8):e513-8. doi: 10.1161/STROKEAHA.110.581918. Epub 2010 Jun 17. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20558831>
- Sibon I, Couprie Y, Menegon P, Bouchet JP, Gorry P, Burgelin I, Calvas P, Orignac I, Dousset V, Lacombe D, Orgogozo JM, Arveiler B, Goizet C. COL4A1 mutation in Axenfeld-Rieger anomaly with leukoencephalopathy and stroke. *Ann Neurol*. 2007 Aug;62(2):177-84.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17696175>

- Vahedi K, Alamowitch S. Clinical spectrum of type IV collagen (COL4A1) mutations: a novel genetic multisystem disease. *Curr Opin Neurol.* 2011 Feb;24(1):63-8. doi: 10.1097/WCO.0b013e32834232c6. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21157337>
 - Volonghi I, Pezzini A, Del Zotto E, Giossi A, Costa P, Ferrari D, Padovani A. Role of COL4A1 in basement-membrane integrity and cerebral small-vessel disease. The COL4A1 stroke syndrome. *Curr Med Chem.* 2010;17(13):1317-24. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20166936>
-

Reprinted from Genetics Home Reference:

<https://ghr.nlm.nih.gov/condition/col4a1-related-brain-small-vessel-disease>

Reviewed: September 2011

Published: March 21, 2017

Lister Hill National Center for Biomedical Communications

U.S. National Library of Medicine

National Institutes of Health

Department of Health & Human Services